Thyroid

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Thyroid function and the risk of fibrosis of the liver, heart and lung in humans: A systematic review and meta-analysis

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ABSTRACT

Background

Fibrotic diseases have an unclear etiology and poor prognosis. Fluctuations in thyroid function may play a role in the development of fibrosis, but evidence is fragmented and inconclusive. This systematic review and meta-analysis aimed to investigate the association of thyroid function with fibrotic diseases of the liver, heart, and lung, in humans.

Methods

We searched Pubmed, Medline Ovid, Embase Ovid, and Web-of-Science **for studies published** from inception to 14 June 2019, to identify observational studies that investigated the association of thyroid function with fibrosis of the liver, heart, and lung, in humans. Study quality was evaluated by Newcastle-Ottawa Scale. The Mantel-Haenszel method was used to pool the odds ratios (ORs) of studies investigating the association of hypothyroidism with liver fibrosis.

Results

Out of 2196 identified articles, 18 studies were included in the systematic review, of which 11 studies reported on liver fibrosis, 4 on myocardial fibrosis, and 3 on pulmonary fibrosis. The population sample size ranged from 36 to 7259 subjects, with median mean age 51 years (range, 36-69) and median percentage of women 53 (range, 17-100). The risk of bias of studies was low to moderate to high. Higher serum thyrotropin and lower thyroid hormone levels were generally associated with higher likelihood of fibrosis. Compared to euthyroidism, overt and subclinical hypothyroidism were associated with a higher likelihood of fibrosis in the liver (6 of 7 studies), heart (3 of 3 studies), and lung (3 of 3 studies). Based on the results of the 7 studies included in the meta-analysis, overt and subclinical hypothyroidism were associated with an increased risk of liver fibrosis (pooled OR, 2.81; 95% confidence interval [CI], 1.74-4.53; heterogeneity, I^2 31.4%; pooled OR, 2.12; CI, 1.45-3.12, heterogeneity, I^2 0% respectively), without evidence of publication bias.

Conclusions

This study suggests that low thyroid function is associated with increased likelihood of chronic fibrotic diseases of the liver, heart, and lung. However, the evidence is mainly based on cross-sectional data. Prospective studies and randomized clinical trials are needed to investigate the potential efficacy of thyroid hormone and its analogues on the occurrence and progression of fibrosis.

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INTRODUCTION

Fibrotic diseases, including liver cirrhosis, hypertrophic cardiomyopathy, and idiopathic pulmonary fibrosis, represent a significant cause of disability and mortality (1-4). The development of fibrosis is attributable to a maladaptive response characterized by the accumulation of extracellular matrix proteins such as collagen and fibronectin (5). Fibrotic elements progressively remodel and destroy the normal tissue architecture, ultimately resulting in organ failure. Hence, nonalcoholic steatohepatitis can progress to decompensated cirrhosis (6); myocardial fibrosis leads to ventricular diastolic dysfunction (7); whereas pulmonary fibrosis contributes to a decline in the lung function (8).

To date, the prognosis of fibrotic diseases remains poor, owing to the poor understanding of its pathogenesis and the lack of effective therapeutic options. Therefore, current research is focused on the identification of novel determinants of fibrosis, which could be further translated into the development of effective treatments (9-11). Among other factors, hypothyroidism has been implicated in the etiology of fibrosis (12-15). Pronounced hypothyroidism is typically characterized by an increased production of mucopolysaccharides, resulting in interstitial fibrosis and extracellular water retention, also known as myxedema (16). Yet, the exact role of thyroid hormones in the development of fibrosis remains unclear as well as controversial. A number of animal studies have reported profibrotic effects of hypothyroidism (13, 17-21); and beneficial effects of thyroid hormone supplementation on fibrosis of the liver (22, 23), heart (24-26), and lung (27). In contrast, other animal studies have observed an attenuation of fibrosis in experimental hypothyroidism (28, 29), and have shown profibrotic effects of thyroid hormone administration (30-34). Similar to animal studies, the results of epidemiological studies are also inconsistent. Some studies suggest a link between thyroid function and the risk of fibrosis of the liver, heart and lung (12, 14, 15), whereas others report no such association (35, 36).

To date, there is a critical lack of literature synthesis concerning the impact of thyroid function on the occurrence and progression of organ fibrosis. Therefore, we aimed to summarize the current evidence regarding the association of thyroid function with fibrosis of the liver, heart and lung in humans.

MATERIALS AND METHODS

Data sources and search strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines for transparent reporting (37). The checklist is provided in Appendix 1. Four electronic databases, including Pubmed, Medline Ovid, Embase Ovid, and Web-of-Science were searched without language restrictions from inception to 14 June 2019, with the help of expert librarians. From the date of the last search, we received monthly updates by the medical library in order to avoid missing new relevant references. The computer-based searches combined terms related to: (I) thyroid function (e.g., thyroid gland, thyroid disease, thyroid function, thyroid hormone, thyrotropin, thyroxine, triiodothyronine, thyronine, hyperthyroidism, thyrotoxicosis, Graves', hypothyroidism, Hashimoto, myxedema, deiodinase); (II) fibrosis of the liver, heart, and lung (e.g., liver fibrosis, nonalcoholic steatohepatitis, lung fibrosis, fibrosing alveolitis, fibrosing interstitial pneumonia, heart fibrosis); and (III) article type (i.e., Editorials, letters to the Editor, erratum, conference papers were excluded). Details of the search strategy are provided in Appendix 2.

Study selection and data extraction

The studies that fulfilled the following criteria were eligible: (I) Observational studies, including cross-sectional studies, prospective studies, case-control studies, nested case-control studies, nested case-cohort studies; (II) Studies that investigated the association of hypothyroidism, hyperthyroidism, or thyroid parameters (i.e., thyroid-stimulating hormone [TSH], free thyroxine [FT_4], free triiodothyronine [FT_3]) with fibrosis of the liver, heart, or lung, in humans; (III) Studies reporting effect estimates (risk ratio, odds ratio or hazard ratio) with 95% confidence intervals (CIs), or correlation coefficients (p-values) used to correlate thyroid function with fibrosis, or mean differences (with standard deviations; p-values) in thyroid function between cases and controls, or mean differences (with standard deviations; p-values) in fibrotic scores between thyroid status categories, or prevalence differences (p-values). Case-reports, letters to the editor, proceedings, conference abstracts, reviews, systematic reviews, meta-analyses, and animal studies were excluded. The studies that focused exclusively on the role of thyroid function-altering

medications on fibrotic diseases were also excluded. There were no restrictions on publication year or language.

Two independent reviewers (AB, SR) screened the titles and abstracts of the citations. The full texts of relevant articles were further obtained and independently evaluated. Any disagreement between the two reviewers regarding inclusion was resolved through consensus or with the help of a third independent reviewer. Full texts and reference lists of the selected articles were hand searched to identify additional studies. A predesigned data collection form was used to extract relevant information from the selected studies, including article source, sample size, demographics of study participants, methods of assessing thyroid function and fibrosis, study results and conclusions.

Quality assessment

The quality of the included studies was assessed separately by two reviewers (AB, SR) using the Newcastle–Ottawa Scale (NOS) for non-randomized studies in meta-analyses (Appendix 3a) (38, 39). The quality of cross-sectional studies was assessed by using an adapted NOS version (Appendix 3b). NOS evaluates the study quality based on 3 domains, namely selection of participants, comparability of study groups, and ascertainment of the exposure or outcome of interest. Each study could have a maximum of 9 stars. Based on the Agency for Healthcare Research and Quality (AHRQ) standards, the quality of the studies was categorized as poor, fair, and good; corresponding to high, moderate, and low risk of bias, respectively (Table 4) (38, 40).

Statistical analyses

For continuous outcomes, summary measures were presented as mean differences. To enhance the comparability among studies, we converted the units of measurements where appropriate. We used odds ratios (ORs) with their 95% CIs as provided by the included articles, or calculated them manually using available information. Fixed-effects Mantel-Haenszel models were used to obtain pooled ORs with 95% CIs for the association of hypothyroidism, overt and subclinical hypothyroidism with liver fibrosis (41). We constructed forest plots, and assessed heterogeneity by using the I^2 statistic, with I^2 ≤25% considered as low, 25%< I^2 <75% as moderate, and I^2 ≥75% as high (42). The possibility of publication bias was assessed by using funnel plots and Egger regression symmetry tests (43). Statistical analyses were performed in Stata version 15.1 (StataCorp LLC, Texas, USA).

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Sensitivity analyses: The following sensitivity analyses were performed: (I) We used random-effects models in order to account for heterogeneity. (II) We excluded the studies that provided unadjusted estimates, thus limiting the meta-analysis to studies that accounted for relevant potential confounders. (III) To assess the impact of individual studies on the overall results, we calculated the pooled risk estimates after removing one by one the studies from the analyses. (IV) In order to account for a possible influence of thyroid medications on our results, the studies on hypothyroidism were stratified in studies including or excluding the thyroid medication users. (V) We performed subgroup analyses by stage of hypothyroidism (i.e., overt or subclinical hypothyroidism). (VI) The studies were stratified based on the source population (non-hospitalized versus hospitalized patients). (VII) We performed subgroup analyses by study design (i.e., cross-sectional or longitudinal studies).

RESULTS

Literature search

The results of the search strategy are presented in Figure 1. After excluding duplicates, we identified 2196 relevant citations; and after further screening of abstracts, 63 potentially relevant articles were identified. Once the full texts of these articles were examined, 18 eligible unique studies were selected (12, 14, 15, 35, 36, 44-56).

Thyroid function and fibrosis of the liver, lung and heart

Table 1 summarizes the main characteristics of the 18 included studies reporting on the association of thyroid function with fibrosis of the liver, lung, and heart. The population sample size ranged from 36 to 7259 subjects (Table 1). The median mean age was 51 years (range, 36-69), and the median percentage of women was 53 (range, 17-100) (Table 1). Of the 18 included studies, 7 studies were performed in Asia (15, 44, 49, 50, 53-55), 6 in the United States (14, 35, 45, 46, 48, 51), 3 in Europe (12, 47, 52), 1 in Africa (56) and 1 in South America (36) (Table 1). Seventeen studies had a cross-sectional or case-control design, and 1 study had a prospective design (Table 1). Ten studies (14, 15, 35, 45, 47-50, 55, 56) included hospitalized patients, 5 studies recruited participants from outpatient clinics (36, 44, 46, 52, 53), and 3 studies included participants from the general population (12, 51, 54) (Table 1). All studies controlled for confounders, except for 2 studies that reported unadjusted estimates (35, 36) (Table 1).

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The studies reported on blood measurements of thyroid function (TSH, FT_4, FT_3) (12, 35, 47, 49, 50, 52, 54-56), overt hypothyroidism (12, 14, 15, 36, 45, 46, 48, 53, 55), subclinical hypothyroidism (12, 44, 50, 51, 55, 56), and subclinical hyperthyroidism (12) (Table 2, Table 3). Of the 13 studies investigating hypothyroidism, 10 studies did not specify the cause of hypothyroidism and 3 studies defined hypothyroidism as Hashimoto`s thyroiditis (Table 2). Several definitions of hypothyroidism were used. In 6 studies, the diagnosis of hypothyroidism was based on a self-reported disease history and use of thyroid hormone replacement therapy (14, 36, 45, 46, 48, 53) (Table 2). Seven studies diagnosed overt and subclinical hypothyroidism based on the serum TSH and FT_4 measurements, after excluding the thyroid medication users (12, 15, 44, 50, 51, 55, 56) (Table 2). Nine studies excluded patients with past thyroid surgery (Table 2).

The outcomes were liver fibrosis (11 studies), myocardial fibrosis (4 studies), and fibrotic pulmonary diseases (3 studies) (Table 1). Of the studies assessing liver fibrosis, 7 studies used liver biopsy (35, 36, 44-47, 53), 3 studies used fibrosis scores (51, 52, 54), and 2 studies used liver elastography (12, 52) (Table 1). Myocardial fibrosis was assessed by cardiac magnetic resonance imaging, using measurements of myocardial longitudinal relaxation time T1-mapping (3 studies) (15, 50, 55), or measurements of late gadolinium enhancement (1 study) (49) (Table 1). The fibrotic pulmonary diseases included IPF (idiopathic pulmonary fibrosis) (2 studies) (14, 56) and chronic hypersensitivity pneumonitis (CHPP) (1 study) (48) (Table 1). IPF and CHPP were diagnosed based on lung biopsy and computed tomography, according to the American Thoracic Society criteria (14, 48, 56) (Table 1).

The results of studies investigating the association of hypothyroidism with liver fibrosis were combined in a meta-analysis. The studies that were included in the meta-analysis used logistic regression to evaluate odds ratios. Due to the heterogeneity in methodology or differences in the assessment of fibrotic diseases, we could not perform quantitative meta-analyses for: (I) studies investigating the association of thyroid parameters with liver fibrosis; (II) studies on myocardial fibrosis; and (III) studies on pulmonary fibrosis.

Liver fibrosis: Eleven studies investigated the association of thyroid status and/or thyroid parameters with liver fibrosis (Table 1). Of these, we identified 7 studies investigating the association of thyroid parameters (TSH, FT_4, FT_3) with liver fibrosis (12, 35, 44, 47, 51, 52,

54) (Table 3). In the general population, increasing TSH levels were associated with higher odds of liver fibrosis (OR, 1.49; CI, 1.04-2.15 per 1 log TSH) (12) (Table 3). In euthyroid subjects, some studies reported no association of thyroid function with liver fibrosis (12, 35, 44, 54) and others reported an association of increasing TSH levels with liver fibrosis (47, 51) (Table 3). We also identified one study investigating subclinical hyperthyroidism and liver fibrosis, but without finding an association (OR, 0.80; CI, 0.04-3.91) (12). Furthermore, we identified studies investigating the association of overt hypothyroidism (5 studies) (12, 36, 45, 46, 53), and subclinical hypothyroidism (3 studies) (12, 44, 51) with liver fibrosis (Table 2). Based on the results of the meta-analysis, the presence of hypothyroidism was associated with a higher risk of liver fibrosis compared to euthyroidism (pooled OR, 2.48; CI, 1.87-3.29, heterogeneity I^2=0%) (Figure 2a). In particular, clinical and subclinical hypothyroidism were associated with a higher risk of liver fibrosis compared to euthyroidism (pooled OR, 2.82; CI, 1.95-4.07, heterogeneity I^2=31.4%; pooled OR, 2.12; CI, 1.45-3.12, heterogeneity I^2=0%, respectively) (12, 36, 44-46, 51, 53) (Figure 2b, Figure 2c). Sensitivity analyses using random-effects models provided similar estimates (pooled OR for overt hypothyroidism, 2.81; CI, 1.74-4.53; pooled OR for subclinical hypothyroidism, 2.12; CI, 1.45-3.12) (Figure 2b, Figure 2c). After sensitivity analyses removing one by one the studies from the analyses, the results did not change substantially (pooled OR for overt hypothyroidism varying from 2.40 [1.52-3.78] to 3.19 [2.16-4.70]; pooled OR for subclinical hypothyroidism varying from 2.10 [1.28-3.43] to 2.16 [1.37-3.41]). After removing the study reporting unadjusted estimates (36), the association of overt hypothyroidism with liver fibrosis became stronger and the heterogeneity was eliminated (pooled OR, 3.19; CI, 2.16-4.70, heterogeneity I^2=0%). The studies that included patients with overt hypothyroidism being treated with thyroid hormones (36, 45, 46, 53) reported smaller ORs (pooled OR, 2.68; CI, 1.84-3.92) compared to the study that excluded thyroid medication users (OR, 6.64; CI, 1.04-23.95) (12). The association of overt hypothyroidism with liver fibrosis was stronger in the studies recruiting participants from the outpatient clinic or general population (pooled OR, 3.06; CI, 1.56-6.0) (12, 36, 46, 53) compared to the study that included hospitalized patients (OR, 2.30; CI, 1.20-4.0) (45). The exclusion of the prospective study (12) from the analyses resulted in slightly smaller

estimates for overt hypothyroidism (pooled OR, 2.68; CI, 1.84-3.92) and subclinical hypothyroidism (pooled OR, 2.12; CI, 1.17-4.01).

Myocardial fibrosis: Four studies investigated the association of hypothyroidism and/or thyroid parameters with myocardial fibrosis (15, 49, 50, 55) (Table 1). Of these, 3 studies consistently showed that overt and subclinical hypothyroidism are associated with a higher degree of diffuse fibrosis than euthyroidism (Table 2) (15, 50, 55). Two studies showed a positive correlation of TSH (correlation coefficients varying from 0.49 to 0.52) and a negative correlation of FT_4 (correlation coefficients -0.48 for both studies) with myocardial fibrosis (50, 55), whereas another study did not find an association (49) (Table 3). Three studies showed a negative correlation of FT_3 with myocardial fibrosis (15, 49, 55) (Table 3).

Pulmonary fibrosis: Three case-control studies investigated the association of hypothyroidism with fibrotic diseases of the lung (14, 48, 56) (Table 2). Overt hypothyroidism was associated with a 2.70 and 2.39 times higher odds of IPF and CHPP than euthyroidism, respectively, after adjusting for potential confounders as BMI, smoking, diabetes, and corticosteroid use (14, 48) (Table 2). Subclinical hypothyroidism was associated with a 8.58 times higher odds of IPF than euthyroidism, but the estimate was unadjusted for potential confounders (56) (Table 2).

Quality assessment

Study bias assessment scores are shown in Table 4. A total of 5 studies scored 5/9 stars, 6 studies scored 6/9 stars, 5 studies scored 7/9 stars, and 2 studies scored 8/9 stars (Table 4). Of the 18 included studies, 8 studies were rated as “poor quality”, 6 studies were rated as “fair quality”, and 4 studies were rated as “good quality” (Table 4).

Assessment of publication bias

The funnel plots for the association of hypothyroidism, overt hypothyroidism, and subclinical hypothyroidism with liver fibrosis are shown in Appendix 4. The Egger test did not indicate significant funnel plot asymmetry (p-values, 0.9, 0.5, and 0.3, respectively) and thus provided no evidence of publication bias, although it should be noted that a maximum of 7 studies were included.

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DISCUSSION

This systematic review and meta-analysis summarize the current evidence regarding the role of thyroid function on fibrosis of the liver, heart and lung in humans. Overall, low thyroid function was associated with increased likelihood of fibrosis of the liver, heart, and lung. The association was consistent, irrespective of the diverse study populations, methodologies and fibrosis locations. The risk of bias of included studies was low to moderate to high.

Overt hypothyroidism was generally associated with higher likelihood of fibrosis compared to subclinical hypothyroidism, suggesting a dose-response relationship. The magnitudes of the associations differed across studies, which may be attributable to the differences in population characteristics, fibrosis locations, fibrosis assessment, and definitions of hypothyroidism used across studies. In general, studies that excluded thyroid medication users (12, 44) reported larger effect estimates compared to the studies that included hypothyroid patients treated with thyroid hormone replacement therapy (14, 45, 46, 48). In the latter group, it is possible that levothyroxine treatment may have reduced the risk of fibrosis, further resulting in an underestimation of the observed associations. The heterogeneity among studies examining the association of overt hypothyroidism with liver fibrosis was eliminated after removing the study by Mazo et al. (36). In this study, the lack of adjustment for confounders and the administration of levothyroxine may have led to an underestimation of the observed associations (36). Studies examining thyroid parameters generally concluded that increasing TSH levels were associated with higher likelihood of fibrosis (12, 47, 50). Even in euthyroid subjects, low-normal thyroid function tended to be associated with increased likelihood of fibrosis, though sometimes not statistically significant (12, 44, 47). This could be explained by insufficient sample sizes or by a lesser fibrotic response of low-normal thyroid function compared to low thyroid function.

The results of this systematic review of observational studies in humans are also supported by previous case reports and experimental studies (57-61). Case series and case reports in humans have indicated a co-occurrence of hypothyroidism and fibrotic diseases of the liver, heart, and lung (57-59). The diffuse myocardial injuries among patients with overt hypothyroidism were reversed by restoring euthyroidism with short-term levothyroxine treatment (60). In patients with severe hypothyroidism, the radiologic abnormalities

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suggestive of lung fibrosis were also reversed after receiving thyroid hormone replacement therapy (61). Furthermore, several animal studies suggested that fibrosis of the liver, heart, and lung, can be promoted by hypothyroidism and can be reversed by the administration of thyroid hormones (17, 18, 20, 24, 27, 62).

Several mechanisms can explain the association of thyroid function with fibrotic diseases, including alterations in collagen gene expression, collagen deposition, activity of fibrogenic cytokines, and redox balance (13, 19-25, 63). Fibrotic diseases of the liver, heart and lung share the common histological feature of extracellular matrix accumulation (64). Experimental hypothyroidism can lead to fibrosis via upregulation of the collagen type I gene expression (13, 19, 20), whereas thyroid hormone administration reduces collagen type I gene expression (22, 24, 25). Thyroid hormones also enhance the matrix metalloproteinase activity, further resulting in a collagen breakdown (65). The transforming growth factor beta (TGFβ), a potent fibrogenic cytokine, is additionally involved in the development of hepatic, myocardial, and pulmonary fibrosis (21, 23, 66, 67). In hypothyroid patients, TGFβ triggers intracellular changes in SMAD proteins, which enter the nucleus, promoting collagen transcription and fibrosis (23). Thyroid hormones, on the other hand, antagonize the progression of fibrosis via inhibiting the TGFβ/SMAD-dependent transcriptional activation (23). Thyroid hormone receptors may play a key role in mediating the aforementioned effects of thyroid hormones on hepatic, myocardial, and pulmonary fibrosis (13, 23, 27). In experimental studies, thyromimetic compounds selective for thyroid hormone receptors have shown antifibrotic properties, whereas genetically ablated thyroid hormone receptors resulted in the development of fibrosis (13, 23, 27). Mitochondrial dysfunction is another mechanism that can explain the link between thyroid function and fibrosis (68, 69). Hypothyroidism has been associated with mitochondrial dysfunction and increased production of reactive oxygen species, which contribute to cell apoptosis and fibrosis (68, 69). This can be opposed by thyroid hormones, which improve mitochondrial function and attenuate oxidative stress (68-70). Furthermore, it may be speculated that autoimmune processes underlying hypothyroidism contribute to the development of fibrosis in the liver, heart and lung. Several studies in this systematic review reported that hypothyroid patients with Hashimoto`s thyroiditis had a higher likelihood of fibrotic diseases compared to euthyroid subjects (15, 50, 55).

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However, none of the studies addressed whether the link between hypothyroidism and fibrotic diseases is independent of thyroid peroxidase antibodies or antithyroglobulin antibodies. Besides the shared pathways linking thyroid function to fibrosis of the liver, heart, and lung, underlying organ-specific mechanisms can play an additional role. For example, a hypothyroid state is associated with dyslipidemia, insulin resistance, and obesity, which in turn promote the development of liver steatosis that can eventually progress to cirrhosis (71-73). Moreover, hypothyroidism-associated lung fibrosis could be due to hypoxia, which improves when the hypothyroidism is treated (27).

One could also hypothesize that health-related problems underlying fibrotic diseases affect thyroid parameters. Severe illnesses (e.g., sepsis, hypoxia, chronic illnesses) may result in “non-thyroidal illness”, a condition which is characterized by normal or low-normal serum TSH, low serum FT3 and low serum FT4 levels (74). Although the exact mechanisms underlying non-thyroidal illness remain unclear, poor health states can stimulate a dysregulation of hypothalamus-pituitary-thyroid axis and alterations in the expression of thyroid hormone receptors, transporters or deiodinases, which can eventually lead to changes in thyroid hormone levels. The results of this systematic review, however, are not likely explained by non-thyroidal illness, because the included studies were not performed in critically ill populations. The studies that were performed in hospitalized populations usually excluded the patients with chronic and decompensated conditions. The other studies were conducted in relatively healthy participants from the general population or outpatient clinics.

To the best of our knowledge, this is the first systematic review, which combines the literature regarding the role of thyroid function on fibrosis of the liver, heart and lung, in humans. In accordance with the NOS scale, we used strict criteria for the quality assessment of the risk of bias. Most of the included studies adjusted for potential confounders, including age and sex. Another strength is the consistency of the results in the setting of diverse study populations. The wide range of ages (mean age ranging from 36 to 69) and ethnicities of participants may increase the generalizability of our conclusions. Furthermore, we were able to perform summary statistics, and combine the available evidence on hypothyroidism and liver fibrosis in a meta-analysis. Sensitivity analyses provided consistent estimates. No evidence of publication bias was observed.

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Several limitations of this systematic review warrant consideration. Most of the included studies were characterized by a cross-sectional design; therefore, we cannot exclude the possibility of reverse causation or bidirectional associations. The results of cross-sectional studies in this systematic review, however, were in line with the results of the prospective study (12) suggesting a temporal association between low thyroid function and fibrosis risk. Additional evidence from experimental studies supports more strongly an effect of hypothyroidism on fibrotic diseases rather than vice-versa (17, 18, 20, 24, 27). Another limitation of this systematic review is that the included studies used several definitions of thyroid dysfunction and different measures of fibrotic outcomes. Nevertheless, results were overall consistent. The studies defining thyroid status based on thyroid function measurements did not have data available with regard to variations in thyroid function over time. Furthermore, the limited number of identified studies illustrates the scarcity of evidence on this topic, especially for myocardial and pulmonary fibrosis.

Future population-based studies examining the association of thyroid dysfunction (i.e., hypothyroidism and hyperthyroidism) with the risk of fibrotic diseases should preferably be characterized by a prospective design and a long-term follow-up period. Adequately powered studies are also needed to clarify whether the risk of fibrosis is affected by the fluctuations within the reference range of thyroid function. Of importance, future randomized clinical trials are warranted to simultaneously examine the potential beneficial effects of thyroid hormone supplementation on fibrosis of the liver, heart and lung. These investigations could eventually promote the development of new therapies against fibrotic diseases. In addition, thyroid disease may also play a role in the development of other fibrotic processes, including idiopathic retroperitoneal fibrosis, primary biliary cirrhosis, and skin fibrosis; but the amount of current evidence is very limited and further research is needed (23, 75, 76). Given the systemic effects of thyroid hormones, future studies may also consider investigating the association of thyroid function with the risk of concomitant fibrotic processes in multiple organs. Finally, future observational and experimental studies need to provide additional insights on the shared and organ-specific mechanisms linking thyroid function to fibrosis of the liver, heart and lung, using mediation analyses and interventional approaches. In particular, it remains uncertain whether the link between thyroid function and fibrotic diseases is independent of thyroid autoimmunity,

hypoxia and chronic illnesses. Given the complexity of the mechanisms underlying fibrosis, future studies may need to unravel the interplay of thyroid hormones with inflammatory, hormonal, metabolic, immune, environmental, genetic, and other putative risk factors of fibrotic diseases.

Conclusions

Our findings suggest that low thyroid function is associated with an increased likelihood of chronic fibrotic diseases of the liver, heart, and lung, in humans. Results were consistent in the setting of diverse study populations. Given the limited amount of prospective evidence on this topic, our study highlights the need for future prospective studies and randomized clinical trials investigating the potential efficacy of thyroid hormone and its analogues on the development of fibrosis. This could eventually lead to the development of novel strategies for the prevention and treatment of the fibrotic diseases.

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Author Disclosure Statement

No competing financial interests exist.

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Table 1. Description of included studies on the association of thyroid function with fibrosis of the liver, heart and lung*

First author, year (Reference)	Country	N	Age (mean)	% Women	Study design	Population	Adjustment/ Matching (if applicable)	Outcome (Assessment)
Thyroid function and liver fibrosis								
Liangpunsakul, 2003 (45)	USA	616	49	59	Case-control	NASH cases and non-NASH controls (Inpatients)	Diabetes, hyperlipidemia, hypertension. Matched for age, sex, race, weight	NASH (85% liver biopsy 15% radiologic)
Mazo, 2011 (36)	Brazil	103	54	70	Cross-sectional	NAFLD patients (Outpatients)	-	NASH (Liver biopsy)
Pagadala, 2012 (46)	USA	246	54	56	Cross-sectional	NAFLD patients (Outpatients)	Diabetes, dyslipidemia, hypertension†	NASH (Liver biopsy)
Carulli, 2013 (47)	Italy	69	44	24	Cross-sectional	Euthyroid NAFLD patients (Inpatients)	Age, sex, chol, BMI, HOMAIR†	NASH (Liver biopsy)
Parikh, 2015 (53)	India	800	NR	NR	Cross-section	NAFLD patients	ALT, AST, BMI Matched by	NASH (Liver

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					al	and subjects without liver disease (Outpatients)	age, gender, BMI	biopsy)
Bano, 2016 (12)	Netherlands	4762	65	57	Prospective	General population	Age, sex, cohort, alcohol, smoking, hypolipidemic drugs, chol, Tg, BMI, hypertension, diabetes	NAFLD with fibrosis (Elastography)
Bril, 2016 (35)	USA	NR	57	17	Cross-sectional	Euthyroid diabetic NAFLD patients (General population and inpatients)	-	NASH (Liver biopsy)
Kim, Kim, 2018 (44)	South Korea	425	53	48	Cross-sectional	NAFLD patients (Outpatients)	Age, sex, BMI, smoking, diabetes, hypertension,	NASH (Liver biopsy)

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							Tg, chol, ratio of visceral and subcutaneous tissue area	
Kim, Yoo, 2019 (51)	USA	7259	46	49	Cross-sectional	General population	Age, sex, race, education, marital status, economic status, smoking, waist circumference, hypertension, diabetes, chol	NASH (Fibrosis score)
Liu Y, 2018 (54)	China	638	50	53	Cross-sectional	General population	Cardiovascular risk factors†	NASH (Fibrosis score)
Manka, 2019 (52)	Germany	144	57	27	Cross-sectional	NAFLD patients (Outpatients)	Hypertension, chol†	Advanced NASH (Fibrosis score, elastography)
Thyroid function and myocardial fibrosis								
Gao, 2016 (15)	China	53	36	100	Cross-sectional	OH and euthyroid subjects (Inpatients)	Matched for age, sex	T1-mapping # (Cardiac MRI)

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Wang, 2016 (49)	China	71	54	33	Cross-sectional	IDCM patients (Inpatients)	Age, diabetes, renal dysfunction, hypertension†	LGE‡ (Cardiac MRI)
Yao, 2018 (50)	China	36	36	86	Cross-sectional	SCH and euthyroid subjects (Inpatients)	Matched for age, sex	T1-mapping # (Cardiac MRI)
Liu M, 2019 (55)	China	82	36	100	Cross-sectional	OH, SCH and euthyroid subjects (Inpatients)	Matched for age, sex	T1-mapping # (Cardiac MRI)
Thyroid function and pulmonary fibrosis								
Oldham, 2015 (14)	USA	392	69	26	Case-control	IPF and COPD patients (Inpatients)	BMI, smoking, diabetes, gastroesophageal reflux, CS. Matched for age, sex, race	IPF (Lung biopsy or CT)
Adegunsoye, 2017 (48)	USA	484	65	58	Case-control	CHPP and asthma patients (Inpatie	BMI, smoking, diabetes, CS use. Matched for age, sex, race	CHPP (Lung biopsy or CT)

						nts)		
Aboelnaga, 2019 (56)	Egypt	80	48	45	Case-control	IPF patients and healthy subjects (Inpatients and outpatients)	Matched for age, sex, BMI, smoking	IPF (Lung CT)

*Information is related to the analyses of interest for our particular research question. †Stepwise strategy: Statistically significant predictors were kept in the model. #T1-mapping of the myocardium assesses diffuse myocardial fibrosis. Increased T1-values reflect a longer relaxation time and a more advanced stage of diffuse fibrosis. ǂLGE imaging is used to assess myocardial fibrosis. Abbreviations: N, total number; USA, United States of America; NASH, nonalcoholic steatohepatitis; NAFLD, nonalcoholic fatty liver disease; chol, total cholesterol; BMI, body mass index; HOMAIR, insulin resistance; NR, not reported; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Tg, triglycerides; OH, patients with overt hypothyroidism; MRI, magnetic resonance imaging; IDCM, idiopathic dilated cardiomyopathy; LGE, late gadolinium enhancement; SCH, patients with subclinical hypothyroidism; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; CS, corticosteroid; CT, computed tomography; CHPP, chronic hypersensitivity pneumonitis.

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Table 2. Description of studies reporting on the association of hypothyroidism with fibrosis of the liver, heart and lung

First author, year (Reference)	Hypothyroidism	Cause of hypothyroidism	Diagnosis of hypothyroidism	Outcome (Reference)	Effect estimate
Liver fibrosis					***OR (CI)***
Liangpunsakul, 2003 (45)	Overt	NS	Previous diagnosis of hypothyroidism, and use of THR	NASH (Non-NASH)	**2.30 (1.20-4.0)**
Mazo, 2011 (36)	Overt	NS	Previous diagnosis of hypothyroidism, and use of THR	NASH (Steatosis)	1.04 (0.34-3.15)
Pagadala, 2012 (46)	Overt	NS	Previous diagnosis of hypothyroidism, and use of THR	NASH (Steatosis)	**3.80 (2.0-6.90)**
Parikh, 2015 (53)	Overt	NS	Previous diagnosis of hypothyroidism, or use of THR	NASH (Steatosis)	**3.79 (1.20-11.1)**
Bano, 2016 (12)	Overt	NS	Biochemical,* no thyroid medications, no thyroid	NASH (Non-NASH)	**6.64 (1.04-23.98)**

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			surgery		
	Subclinical	NS	Biochemical,* no thyroid medications, no thyroid surgery	NASH (Non-NASH)	**2.14 (1.04-4.07)**
Kim, Kim, 2018 (44)	Subclinical	NS	Biochemical,† no thyroid medications	NASH (Steatosis)	**2.17 (1.17-4.01)**
Kim, Yoo, 2019 (51)	Subclinical	NS	Biochemical,† no thyroid medications	NASH (Non-NASH)	**2.05 (1.01-4.16)**
Myocardial fibrosis					***Mean difference [ms] in T1-mapping (CI)***#
Gao, 2016 (15)	Overt	Hashimoto	Biochemical,* no thyroid medications, no thyroid surgery	T1-mapping	*T1-LVAW,* **137 (103-171);** *T1-IVS,* **127 (87-167);** *T1-LVIW,* **117 (80-153);** *T1-LVLW*, **119 (84-**

					154)
Yao, 2018 (50)	Subclinical	Hashimoto	Biochemical,* no thyroid medications, no thyroid surgery	T1-mapping	*T1-LVAW,* **66 (26-106)***; T1-IVS,* **66 (28-104);** *T1-LVIW,* **61 (21-101);** *T1-LVLW,* **70 (29-111)**
Liu M, 2019 (55)	Overt	Hashimoto‡	Biochemical,* no thyroid medications, no thyroid surgery	T1-mapping	*T1-LV***, 234 (207-261)**
	Subclinical	Hashimoto‡	Biochemical,* no thyroid medications, no thyroid surgery	T1-mapping	*T1-LV***, 48 (13-83)**
Pulmonary fibrosis					***OR (CI)***
Oldham, 2015 (14)	Overt	NS	Use of THR, no thyroid surgery	IPF (COPD)	**2.70 (1.31-5.54)**
Adegunsoye, 2017 (48)	Overt	NS	Use of THR, no thyroid	CHPP (Asthma)	**2.39 (1.36-**

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			surgery		**4.20)**
Aboelnaga, 2019 (56)	Subclinical	NS	Biochemical, no thyroid medications, no thyroid surgery	IPF (No pulmonary disease)	**8.58 (1.83-40.18)**

*Thyroid status categories were defined based on TSH (thyroid-stimulating hormone) and FT_4 (free thyroxine) measurements. Subclinical hypothyroidism was diagnosed as increased serum TSH levels and normal serum FT4 levels. Clinical hypothyroidism was diagnosed as increased serum TSH levels and decreased serum FT4 levels. †Thyroid function was categorized into strict-normal (TSH 0.4-2.5 mIU/L) (reference), low-normal (TSH 2.5-4.5 mIU/L), and subclinical hypothyroidism (TSH >4.5 mIU/L). # Indicates mean difference (95% confidence interval) in T1 values between hypothyroid patients and euthyroid subjects. T1-mapping of the myocardium assesses diffuse myocardial fibrosis. Increased T1-values reflect a longer relaxation time and a more advanced stage of diffuse fibrosis. Cases had positive thyroid peroxidase antibodies. ‡Cases had positive thyroid peroxidase antibodies and positive antithyroglobulin antibodies. Abbreviations: OR, odds ratio; CI, 95% confidence interval; NS, not specified; THR, thyroid hormone replacement therapy; NASH, nonalcoholic steatohepatitis; ms, milliseconds; T1, myocardial longitudinal relaxation time; T1-LVAW, T1-left ventricular anterior wall; T1-IVS, T1-interventricular septum; T1-LVIW, T1-left ventricular inferior wall; T1-LVLW, T1-left ventricular lateral wall; T1-LV, left ventricular myocardial T1; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; CHPP, chronic hypersensitivity pneumonitis.

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Table 3. Description of studies reporting on the association of thyroid parameters (TSH, FT_4, FT_3) with fibrosis of the liver, heart and lung [a]

First author, year (Reference)	Thyroid function [b]	Outcome (Reference category)	TSH	FT_4	FT_3
Liver fibrosis					
Carulli, 2013 (47)	Euthyroid	NASH (Steatosis)	**OR (CI), 2.74 (1.15; 6.53)** per 1 mU/L		
			MD (CI), 0.54 (0.13; 0.94) mU/L	MD (CI), 0.05 (-0.04; 0.14) ng/dl	MD (CI), 0.11 (-0.17; 0.38) pmol/l*
Bano, 2016 (12)	Full range	NASH (non-NASH)	**OR (CI), 1.49 (1.04; 2.15)** per 1 logTSH	OR (CI), 0.59 (0.13; 2.59) per 1 ng/dl	
	Euthyroid		OR (CI), 1.13 (0.63; 2.03)	OR (CI), 0.81 (0.11; 5.75)	
Bril, 2016 (35)	Euthyroid	NASH (Steatosis)		Prevalence of NASH from lowest to highest FT_4 quintiles, 71%, 59%, 61%, 76%, 80% (p, 0.28)	
Kim, Kim, 2018 (44)	Euthyroid [c]	NASH (Steatosis)	Low-normal TSH versus strict-normal TSH: OR (CI),		

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			1.33 (0.78; 2.24)		
Kim, Yoo, 2019 (51)	Euthyroid [c]	NASH (non-NASH)	Low-normal TSH versus strict-normal TSH: **OR (CI), 1.94 (1.10; 3.44)**		
Liu Y, 2018 (54)	Euthyroid	NAFLD with fibrosis (Steatosis)	MD (CI), -0.20 (-1.06; 0.65) mU/L	MD (CI), 0.002 (-0.09; 0.10) ng/dl†	**MD (CI), 0.13 (0.01; 0.25)** pmol/l OR (CI), 1.18 (1.03; 1.35) per 1 pmol/l
Manka, 2019 (52)	Full range	Advanced NASH (Steatosis)	MD (CI), 0.26 (-0.26; 0.78) mU/L		**MD (CI), -0.84 (-1.28; -0.39)** pmol/l# **OR (CI), 0.32 (0.14; 0.67)** per 1 pmol/l#
Myocardial fibrosis					
Gao, 2016 (15)	Full range	T1-mapping [d]			**r, -0.55, p<0.0001**
Wang, 2016 (49)	Full range	LGE (no LGE) [e]	OR (CI), 0.98 (0.93; 1.04) per 1 mU/L logTSH	OR (CI), 0.37 (0.05; 2.75) per 1 ng/dl	**OR (CI), 0.28 (0.12; 0.69)** per 1 pmol/l*
Yao, 2018 (50)	Full range	T1-mapping	**r, 0.49 (p, 0.002)**	**r, -0.48 (p, 0.003)**	
Liu M, 2019 (55)	Full range	T1-mapping	**r, 0.52 (p<0.001)**	**r, -0.48 (p<0.001)**	**r, -0.40 (p, 0.002)**

Pulmonary fibrosis				
Aboelnaga, 2019 (56)	Full range	IPF (No pulmonary disease)	**MD (CI), 0.74 (0.21; 1.27)** mU/L	MD (CI), 0.03 (-0.17; 0.22) ng/dl

[a] The effect estimates in this table are presented as: (I) odds ratio for the association of thyroid parameters with fibrosis; (II) mean difference in thyroid parameters between cases and controls; (III) correlation coefficient used to correlate thyroid parameters with T1-mapping; and (IV) prevalence of fibrotic disease throughout the range of thyroid parameters. [b] The reported estimates correspond to the euthyroid range or the full range of thyroid function. [c] Thyroid function was categorized into strict-normal (TSH 0.4-2.5 mIU/L) (reference), low-normal (TSH 2.5-4.5 mIU/L), and subclinical hypothyroidism (TSH >4.5 mIU/L). [d] T1-mapping of the myocardium assesses diffuse myocardial fibrosis. Increased T1-values reflect a longer relaxation time and a more advanced stage of diffuse fibrosis. [e] LGE imaging is used to assess myocardial fibrosis. *Converted from pg/ml. †Converted from pmol/l. #Converted from ng/l. Abbreviations: TSH, thyroid-stimulating hormone; FT_4, free thyroxine; FT_3, free triiodothyronine; NASH, nonalcoholic steatohepatitis; OR, odds ratio; CI, 95% confidence interval; MD, mean difference; NAFLD, non-alcoholic fatty liver disease; LGE, late gadolinium enhancement; r, correlation coefficient; IPF, idiopathic pulmonary fibrosis; T1, myocardial longitudinal relaxation time.

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Table 4. Quality Assessment Scale

First author, year (Reference)	Selection (maximum 4 stars)	Comparability (maximum 2 stars)	Exposure or outcome (maximum 3 stars)	Total number of stars	Quality rating
Liangpunsakul, 2003 (45)	***	**	*	6/9	Poor
Mazo, 2011 (36)	***		***	6/9	Poor
Pagadala, 2012 (46)	*	**	***	6/9	Poor
Carulli, 2013 (47)	**	**	***	7/9	Fair
Parikh, 2015 (53)	***	**	***	8/9	Good
Bano, 2016 (12)	****	**	**	8/9	Good
Bril, 2016 (35)	**		***	5/9	Poor
Kim, Kim, 2018 (44)	**	**	***	7/9	Fair
Kim, Yoo, 2019 (51)	***	**	**	7/9	Good
Liu Y, 2018 (54)	***	**	**	7/9	Good
Manka, 2019 (52)	**	*	**	5/9	Fair
Gao, 2016 (15)	*	*	***	5/9	Poor
Wang, 2016 (49)	*	**	***	6/9	Poor
Yao, 2018 (50)	**	*	***	6/9	Fair
Liu M, 2019 (55)	**	*	***	6/9	Fair
Oldham, 2015 (14)	**	**	*	5/9	Poor
Adegunsoye, 2017 (48)	*	**	**	5/9	Poor
Aboelnaga, 2019 (56)	**	**	**	6/9	Fair

†The thresholds for converting the Newcastle-Ottawa Scale (NOS) scores into the Agency for Healthcare Research and Quality (AHRQ) standards were: (I) Good quality: 3 or 4 stars in the selection domain AND 1 or 2 stars in the comparability domain AND 2 or 3 stars in the exposure/outcome domain. (II) Fair quality: 2 stars in the selection domain AND 1 or 2

stars in the comparability domain AND 2 or 3 stars in the exposure/outcome domain. (III) Poor quality: 0 or 1 star in the selection domain OR 0 star in the comparability domain OR 0 or 1 stars in the exposure/outcome domain.

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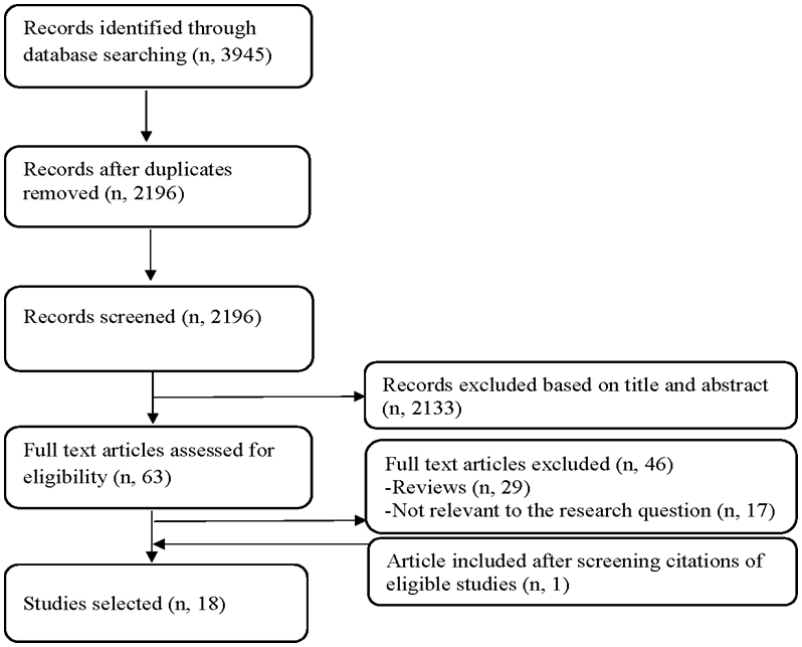
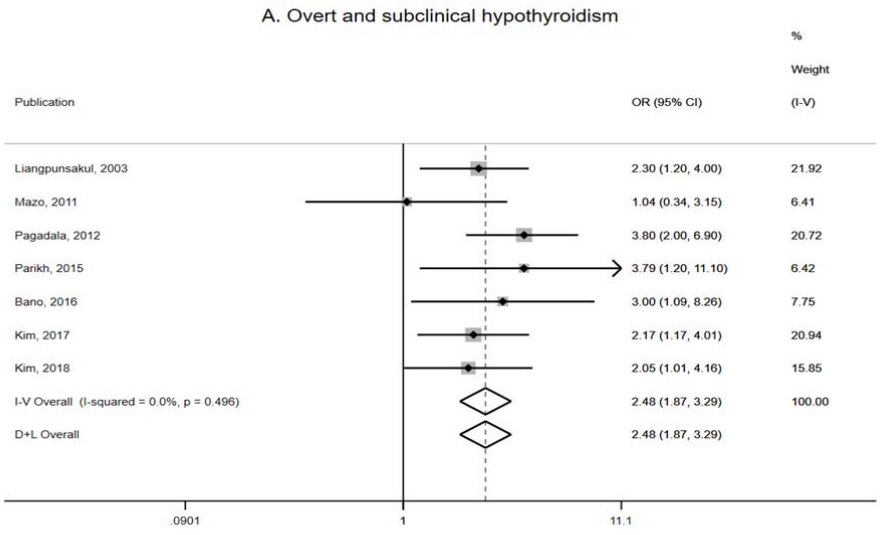


Figure 1. Flowchart for study inclusion, adapted from the PRISMA statement



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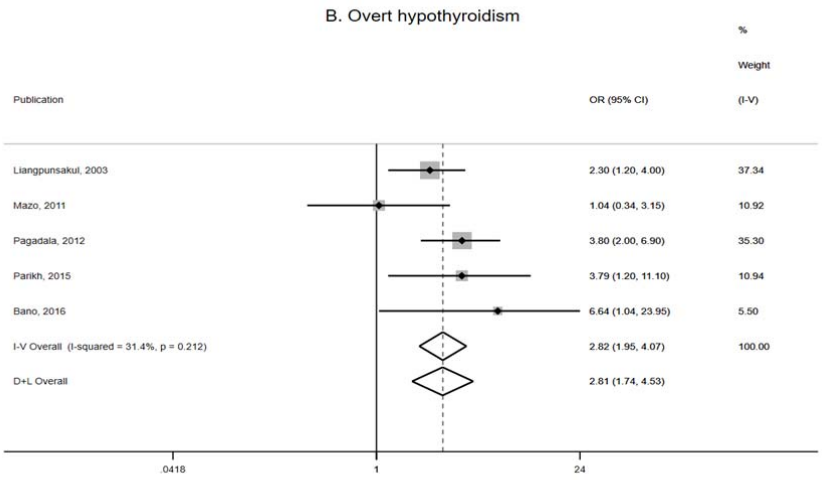

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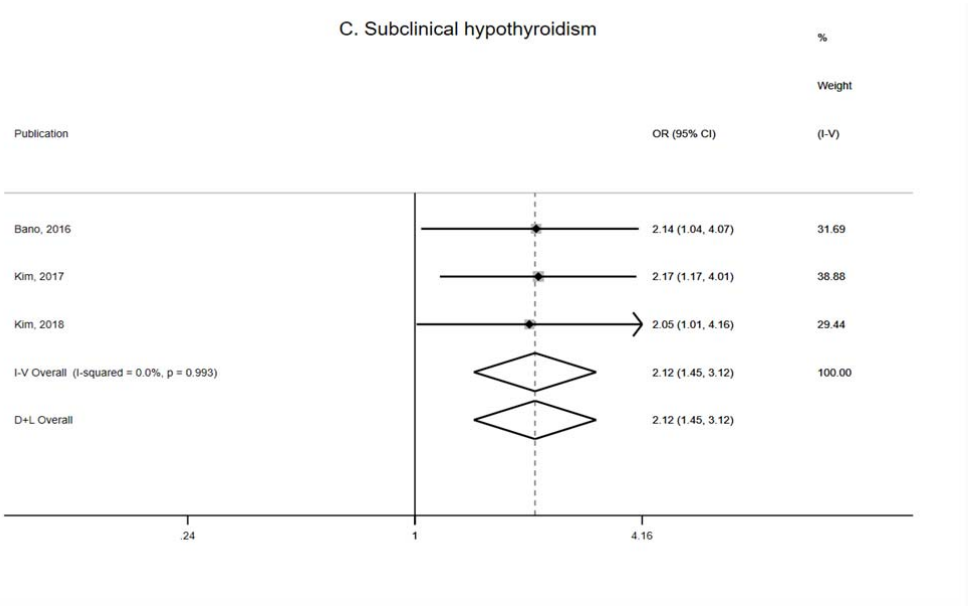

Figure 2. Forest plots for the association of hypothyroidism with liver fibrosis. a. Overt and subclinical hypothyroidism; b. Overt hypothyroidism; c. Subclinical hypothyroidism. Abbreviations: OR, odds ratio; CI, confidence interval; I-V, inverse variance (fixed) method; D+L, Der Simonian and Laird (random-effects) method; I-squared, test for heterogeneity.

SUPPLEMENTAL MATERIAL

Appendix 1. PRISMA 2009 checklist.

Section/Topic		Checklist item	Page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons,	6

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		outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	https://boris.unibe.ch/132182/; https://www.crd.york.ac.uk/PROSPERO Registration number: CRD42019142703
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6-7, Appendix 2

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Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7, Appendix 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8, Appendix 3, Appendix 4
Summary measures	13	State the principal summary measures (e.g., risk ratio,	8

		difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

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Appendix 1 (continued). PRISMA 2009 Checklist.

Section/Topic		Checklist item	Page
METHODS			
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8, Appendix 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9, Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	13, Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	11-12, Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	13, Appendix 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12

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DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Appendix 2. Supplemental information on Search strategy

Search in Pubmed

(((Thyroid*[Title/Abstract] OR hyperthyro*[Title/Abstract] OR Hypothyro* [Title/Abstract] OR thyronine* [Title/Abstract] OR Hashimoto[Title/Abstract] OR thyroid-stimulating hormone [Title/Abstract] OR "free thyroxine"[Title/Abstract] OR Graves[Title/Abstract] OR thyrotropin[Title/Abstract] OR deiodinase[Title/Abstract] OR triiodothyronine[Title/Abstract] OR myxedema[Title/Abstract] OR thyrotoxicosis[Title/Abstract] OR hyperthyroxinemia [Title/Abstract])) AND (Fibrosis[Title/Abstract] OR fibrotic[Title/Abstract] OR fibrosing[Title/Abstract] OR fibroblast[Title/Abstract] OR "non-alcoholic steatohepatitis"[Title/Abstract] OR "nonalcoholic steatohepatitis"[Title/Abstract])) AND (Heart [Title/Abstract] or cardiac [Title/Abstract] or cardiovascular[Title/Abstract] or lung [Title/Abstract] or pulmonary [Title/Abstract] or liver [Title/Abstract] or hepatic[Title/Abstract] or endocardium [Title/Abstract] or myocardium [Title/Abstract] or pericardium[Title/Abstract])

Search in Medline Ovid

((exp thyroid gland/ or hyperthyroxinemia/ or hyperthyroidism/ or hypothyroidism/ or thyroid function tests/
or thyroxine/ or thyroid hormones/ or thyrotropin/ or thyroxine/) OR (Thyroid* or hyperthyro* or Hypothyro* or free thyroxine or thyroid-stimulating hormone or Graves or thyrotropin or thyroxin or deiodinase or hashimoto or triiodothyronine or thyronine* or myxedema or thyrotoxicosis or hyperthyroxinemia).ab,ti.) AND ((Fibrotic or fibrosis or non-alcoholic steatohepatitis or nonalcoholic steatohepatitis or fibrosing).ab,ti. OR fibroblast.mp or fibrosis/ or exp pulmonary fibrosis/ or exp endomyocardial fibrosis/ or idiopathic pulmonary fibrosis/) AND (Heart or cardiac or endocardium or myocardium or pericardium or lung or pulmonary or liver or hepatic or cardiovascular).ab,ti. NOT (congress or editorial or guideline or letter or news or Published Erratum or conference or comment).pt.

Search in Embase Ovid

((exp thyroid gland/ or exp thyroid disease/ or exp thyroxine/ or exp thyroid function/ or thyroid hormone/

or thyrotropin/ or thyroxine/ or exp thyroid hormone blood level/ or exp thyroid gland examination/) or (Thyroid* or hyperthyro* or Hypothyro* or free thyroxine or Graves or thyrotropin or thyroxin or deiodinase or hashimoto or triiodothyronine or thyronine* or myxedema or thyrotoxicosis or hyperthyroxinemia).ab,ti.) AND ((Fibrotic or fibrosis or non-alcoholic steatohepatitis or nonalcoholic steatohepatitis or fibroblast).ab,ti. Or (exp fibrosing alveolitis/ or exp fibrosing interstitial pneumonia/ or exp heart muscle fibrosis/ or exp liver fibrosis/ or exp lung fibrosis/)) AND ((Heart or cardiac or endocardium or myocardium or pericardium or lung or pulmonary or liver or hepatic or cardiovascular).ab,ti.) NOT (Editorial or Letter or Note or Erratum or Conference Paper or Conference Abstract or Conference Review).pt.

Search in Web-of-Science

(TS=(Thyroid* or hyperthyro* or Hypothyro* or “free thyroxine” or thyroid-stimulating hormone or Graves or thyrotropin or deiodinase or triiodothyronine or myxedema or thyrotoxicosis or hyperthyroxinemia or thyronine* or hashimoto)) AND (TS=(Fibrosis or fibrotic or fibroblast or non-alcoholic steatohepatitis or nonalcoholic steatohepatitis or fibrosing)) AND (TS=(Heart OR cardiovascular or cardiac OR endocardium OR myocardium OR pericardium OR lung or pulmonary OR liver OR hepatic)) AND DOCUMENT TYPES: (Article)

Appendix 3. Quality Assessment Scale for included studies

Appendix 3a. Newcastle-Ottawa Quality Assessment Scale for case-control studies

Selection (max 4 stars)

1) *Is the case definition adequate?*

a. yes, with independent validation*

b. yes, eg, record linkage or based on self-reports

c. no description

2) *Representativeness of the cases*

a. consecutive or obviously representative series of cases*

b. potential for selection biases or not stated

3) *Selection of controls*

a. community controls*

b. hospital controls

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c. no description

4) *Definition of controls*

a. no history of disease (end point)*

b. no description of source

Comparability (max 2 stars)

1) *Comparability of cases and controls on the basis of the design or analysis*

a. study controls for the most important factors*

b. study controls for any additional factor**

Exposure (max 3 stars)

1*) Ascertainment of the exposure*

a. secure record (eg, surgical records)*

b. structured interview where blind to case/control status*

c. interview not blinded to case/control status

d. written self-report or medical record only

e. no description

2) *Same method of ascertainment for cases and controls*

a. yes*

b. no

3) *Non-response rate*

a. same rate for both groups*

b. non-respondents described

c. rate different and no designation

Appendix 3b. Adapted Scale from the Newcastle-Ottawa Quality Assessment Scale for cohort studies

Selection (max 4 stars)

1) Representativeness of the exposed cohort

a. Truly representative of the average in the target population (all subjects or random sampling)*

b. Somewhat representative of the average in the target population (non-random sampling)*

c. Selected group of users

d. No description of the derivation of the cohort

2) *Sample size*

a. Justified and satisfactory*

b. Not satisfied

3) *Ascertainment of the exposure (risk factor)*

a. Secure record (eg, medical records)*

b. Structured interview*

c. Written self-report

d. No description of the measurement tool

4) *Non-respondents*

a. Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory*

b. The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory

c. No description of the response rate or the characteristics of the respondents and the non-respondents

Comparability (max 2 stars)

1) *The subjects in the different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.*

a. Study controls for the most important factors (age, sex)*

b. Study controls for additional relevant factors**

c. Inadequate degree of control

Outcome (max 3 stars)

1) *Assessment of the outcome*

a. Independent or blind assessment stated in the paper, or confirmation of the outcome by reference to secure records (eg, X-rays, medical records)**

b. Record linkage (eg, identified through ICD codes on database records)**

c. Self-report (ie, no reference to original medical records or X-rays to confirm the outcome)*

d. No description

2) Statistical test

a. The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including the probability level (p-value)*

b. The statistical test is not appropriate, not described or incomplete.

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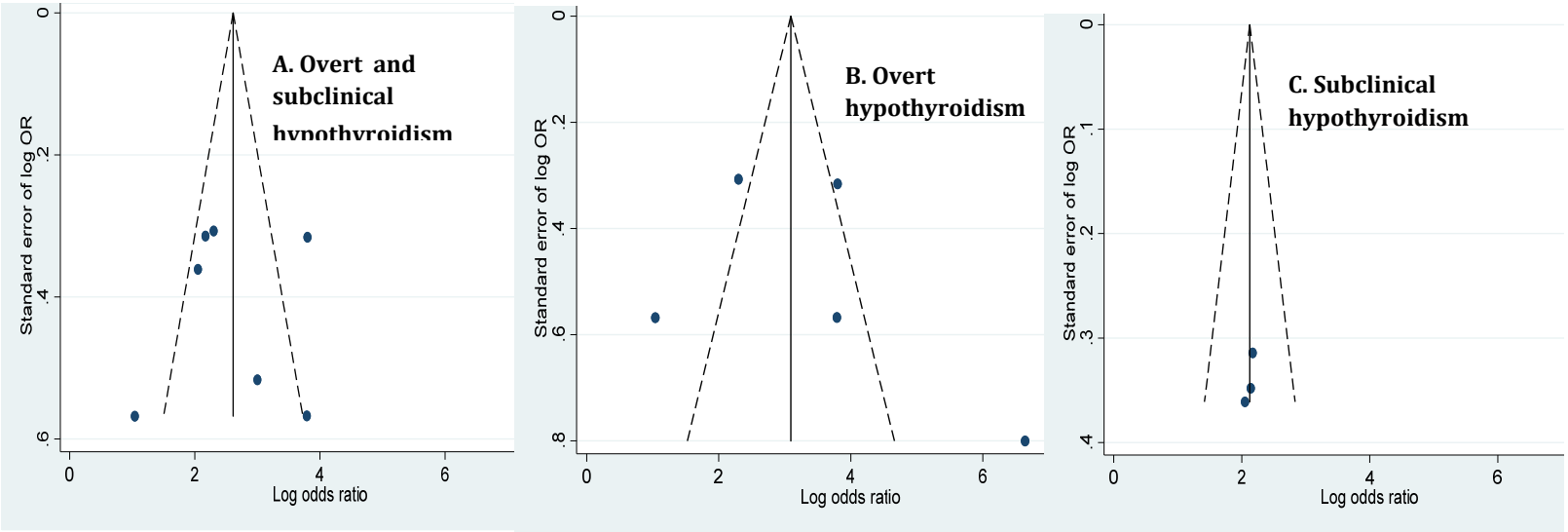
Appendix 4. Funnel plots on the association of hypothyroidism with liver fibrosis. The log odds ratios (ORs) are plotted against the standard error of the logarithm of the OR. The dashed lines depict the logarithm of the summary OR with its 95% confidence interval.



Thyroid
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